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Efficacy of DMSA Therapy in a Sample of Arab Children with Autistic Spectrum Disorder

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ABSTRACT

Objective: *the aim of this study was to provide evidence that DMSA detoxification treatments cause a reduction of the heavy metal burden in the autistic, and that this reduction lessens neurological symptoms associated with ASD (Autistic Spectrum Disorder).*

Method: *The participants were 44 children, age 3 to 9 years of age, with Autistic Spectrum Disorder (ASD) according to Diagnostic and Statistical Manual of Mental Disorders 4t Edition, (DMS-IV). The severity of the autistics symptomatologiy had been measured by the Childhood Autism Rating Scale (SCARS). We collected urine samples before and after the DMSA challenge test, comparing urine metal output. We also compared the results of the DMSA detoxification(=the urine challenge test) with behavioral effects, typical for ASD.*

Results: *The DMSA challenge test increased the urine metal output for a number of potentially toxic metals. Statistically significant difference were noted between the baseline urine and DMSA challenge test regarding the level of cadmium, mercury, and lead (P=0.006, P=0.049, and P=0.008 respectively). We also noted that behavioral effects, typical for ASD (autism spectrum disorders) were reduced with this method of detoxification. A comparison between CARS Subscales and Total Score before and after a 6-month chelation program showed greatest improvements for Verbal and nonverbal communication (P <0.001), Taste, Smell and Touch (P 0.001) and Relating to People (P 0.005). Other improvements were noted for Adaptation to Change and Improvement.*

Conclusion: *DMSA chelation increased the urinary output of toxic and neurotoxic metals. Our data supports evidence that detoxification treatment with oral DMSA has beneficial effect on ASD patients.*

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INTRODUCTION

Autism is a neuro-developmental disorder characterized by qualitative impairments in social interaction and communication, along with restricted activities and interests (1).

The pathophysiological etiologies which precipitate autism symptoms remain elusive and controversial in many cases, but both genetic and environmental factors (and their interactions) have been implicated. One environmental factor that has received significant attention is the body burden of mercury, lead, and other toxic metals (2).

The etiology of autism remains unclear; both environmental and genetic factors have been suggested. Because heavy metals disrupt enzyme functions and cellular signaling processes and generate oxidative stress leading to apoptosis, they could play either a fundamental or a modulating role in the etiology of autism (3).

Heavy metal toxicity can occur from either a high exposure or a decreased ability to excrete heavy metals, with the latter case seeming to be the primary issue in autism. The primary mechanism for excreting mercury and some other toxic metals from the body involves binding to glutathione and then being excreted in the bile (4). Infants are especially vulnerable to metal poisoning because they are poor excretors due to low production of glutathione (5).

The individual burden of toxic metals was assessed based on urinary excretion, both before and after taking oral dimercaptosuccinic acid (DMSA). DMSA is an approved medication, considered safe and effective for treating lead intoxication incases meeting toxic criteria.

In addition, DMSA is widely used off-label for other metal exposures, for example, mercury. It acts by forming sulfhydryl linkages to divalent metal cations, forming a chelated metal complex which is excreted in the urine (6). It is considered an efficient chelating agent, safe for children (7).

Soden et al. (8) asserted that DMSA provoked excretion tests fail to yield evidence of an excess body burden of arsenic (As), cadmium (Cd), and mercury (Hg) in children with autism and the study by Kern et al. (9) on toxicity biomarkers in autism spectrum disorder suggests that increased levels of urinary porphyrins are associated with mercury toxicity. In the Kern study, mercury (Hg) excretion rate was reported to be six-fold higher in children with ASD, compared to healthy controls. The study hypothesized that heavy metals play a role in the development of autism and that further studies on urinary metal excretion are warranted (9).

We used the oral chelator 2,3-dimercaptosuccinic acid (DMSA) to stimulate heavy metal mobilization in children with autistic spectrum disorders (ASD), and correlated urine excretion results to determine how behavioral symptoms are affected. We noticed that the severity of a child's autistic symptoms improves after treatment with this "metal-removing therapy". This is in support of previous studies by the authors which indicate that heavy metal exposure is prevalent in autistic children and related to autistic symptoms (10). ❑

OBJECTIVE

This study examines whether dimercaptosuccinic acid DMSA, an oral chelating agent that removes lead, mercury and other metals from the body, is beneficial for children with autism. The study aimed to evaluate how DMSA therapy affects behavior.

Subjects and Criteria

The participants were 44 Autistic spectrum disorder (ASD) children: 37 boys and 7 girls between the age of 3 and 9 years. Of the total 44 patients, 39 were diagnosed as autistic; two children had been diagnosed with Asperger Syndrome, and three with pervasive developmental disorder (NOS).

The children were either diagnosed previously by other psychiatrists, psychologists, and developmental pediatricians or were suspected by their parents as being autistic. All children attended the child psychiatric clinic of the Erfan Psychiatric Hospital in Jeddah, KSA. Samples were collected during the period of June 2006 to September 2010. All parents signed written informed consent form.

The following entry criteria were applied:

(1) No mercury dental amalgam.
(2) No previous use of DMSA(what) or other prescription chelators.
(3) No anemia or current treatment for iron-deficiency anemia.
(4) No known allergies to DMSA.
(5) No liver or kidney disease.
(6) Children are well hydrated, receiving adequate daily intake of water.

Exclusion criteria

They included refusal to participate, physically handicapped children and children with progressive neurological disorders and unstable epilepsy. We excluded children who were taking regular medications including stimulants, anticonvulsants, and atypical antipsychotic drug.

All of the children admitted to the study received routine childhood vaccinations. All autistic children were subjected to a full clinical child psychiatric sheet for diagnosis of autism spectrum disorder and exclusion of other psychiatric disorder according to Diagnostic and Statistical Manual of Mental Disorders 4th Edition, (DSM-IV) (11).

The severity of autistic symptomatology was measured by the Childhood Autism Rating Scale (CARS), translated by El-Dafrawi. It consists of 15 categories, each rated on a four-point scale. The individual is considered non-autistic when his total score falls in the range of 15-29, mild-to-moderately autistic when his total score falls in the range of 30-36, and severely autistic when his total score falls in the range of 37-60 (12,13).

Reassessment of severity of autistic criteria had been done six months after treatment with the chelating substance DMSA using the Childhood Autism rating Scale CARS. ❑

METHOD

To avoid nutritional inadequacies, the psychiatric clinic provided nutritional supplements, including a multimineral-vitamin-amino acid complex in powder form and zinc gluconate (15mg) previous to chelation. Clinic staff members were in charge of distributing these supplements on a daily basis for three months prior to chelation.

Before DMSA was administered, renal function and normal blood chemistry tests were performed at Erfan Hospital Clinical Laboratory. We also tested the toxic metal content in unchallenged urine samples (baseline urine) as follows:

Baseline urine (first morning urine):

Prior to the DMSA urine challenge, urine samples were collected from all children in the early morning. To avoid contamination, urine collection cups and tubes had been provided to the Centre by Micro Trace Minerals Laboratories of Germany At the laboratory, samples were acid-digested with certified metal-free acids involving closed vessel microwave digestion. For sample dilution ultrapure water was used. Testing was performed via inductively coupled plasma with mass spectrometry (ICP-MS), utilizing cell technique. Certified urine standards and in-house standards were used to validate result (14).

DMSA urine challenge test:

We prepared the children for the challenge test as follows:

- Three days prior to the DMSA challenge test, no fish was eaten.
- Two days prior, all nutritional supplements were stopped.
- On the day of chelation, DMSA was administered in doses of 10 mg/kg body weight for each child. The oral intake was with one cup of water, on an empty stomach.
- Children were able to eat 2 hrs after the oral intake.
- Urine collection was for a total of 4 hours after the oral intake of DMSA.
- Urine samples were mailed via special delivery to Micro Trace Mineral laboratory for assessing toxic metals excretion (14).

Thereafter, according to the management plan, all children were advised to take one single dose of DMSA per month, specifically 10 mg/kg body weight for a total of 6 months.

Statistical Analysis:

Special data files were developed in the computer corresponding to the available data using Excel program 2010. These data were converted and manipulated by using SPSS software program version 17.0. Data were analyzed: characteristics of the sample was presented; mean and standard deviation was estimated as regarding age, developmental milestones in months and numbers and percentages were calculated in regards to sex distribution, type of diagnosis and classification of the test group as regarding CARS total score (mild, moderate and severe). We compared the pre- and post-DMSA results, t test and p value were calculated, and we also compared CARS subscales and total score before and after the 6-month regimen of monthly DMSA chelation treatment, using the same statistical tests to identify the statistically significant difference between groups. Correlation between urine toxic metal lev-

els and subscales scores and total score of CARS was done among cases as a whole. Those correlations were done to test the positive and negative relations between the two variables. The Pearson test was done and the p value was calculated. The relations and correlations were considered statistically significant when $p < 0.05$ and considered highly statistically significant if $p < 0.01$. Tables were presented by using the same SPSS program (15). The level of significance was set at $p < 0.05$. ❑

RESULTS

Table 1 shows that 37 (84%) of the sample were boys in contrast to 7 (16%) girls. The mean age of the whole sample was 5.11±1.57. Thirty-nine children were diagnosed as autistic, 2 (4.5%) with Asperger Syndrome, and 3 (6.9%) were diagnosed PDD (NOS). The mean age of sitting was (6.77±0.96), crawling (10.41±1.65), walking (13.70±1.49), and talking (12.56±4.03).

We need to point out that in nonexposed individuals, the urine metal excretion under non-challenged situations provides inconspicuous results. If food, drink and the environment are relatively metal-free, baseline urine values fall within the reference range as listed in Table 1 and 2. The reference ranges employed and listed here are provided by environmental agencies such as the UBA (Umweltbundesamt) and WHO (World Health Organisation).

For this autistic group, the baseline urine concentration of all metals tested exceeded the given reference range. Significant deviations were noted for Aluminum, Arsenic, Chromium, Nickel and Lead. This indicates immediate exposure.

There were statistical significant difference between the Baseline urine and the DMSA challenge test regarding the level of cadmium, mercury, and lead. This indicates that DMSA stimulates binding and excretion of these metals. We could see no indication from our data that DMSA affects arsenic, chromium, antimony, nickel, uranium and vanadium. In fact, when comparing the mean and standard deviation (SD) of baseline vs challenge values, DMSA administration did not affect these metals (As, Cr, Sb, Ni, U, V). In fact, it slightly lowered urinary excretion.

This raises the question regarding exposure, strengthening the hypothesis that metal exposure in autistic groups is often immediate, possibly caused by metal-rich food, drink and the environment.

There was a significant positive correlation between Baseline urine Aluminum & body use, taste, smell, touch responses, and Total CARS. This indicates that a higher aluminum exposure is associated with increased impairment in these body functions and higher Total CARS.

There was a significant positive correlation between Baseline urine Arsenic & Verbal communication. This means that a higher arsenic exposure is associated with impairment in verbal communication.

There was a significant positive correlation between Baseline urine Cadmium & taste, smell and touch responses. This indicates that cadmium exposure impairs taste, smell, and touch responses.

		Number	percentage	Mean	S.D.
Total participants		44	100		
Male		37	84		
Female		7	16		
Age				5.11	1.57
Diagnosis	Autism	39	88.6%		
	Asperger Syndrome	2	4.5%		
	PDD (NOS)	3	6.9%		
Developmental milestones				6.77	0.96
(in months)	Sitting			10.41	1.65
	Crawling			13.70	1.49
	Walking			12.56	4.03
	Talking	20	45.5		
CARS (mild-moderate)		19	43.2		
CARS (severe)					

TABLE 1. Sample Characteristics.

There was a significant positive correlation between Baseline urine Chromium & body use, auditory response, and taste, smell, touch responses. This means that the higher chromium exposure is associated with impairment in body use, auditory responses, and taste, smell, touch responses.

There was a significant positive correlation between Baseline urine Mercury & taste, smell & touch responses. Mercury exposure is thus associated with impairment in taste, smell, and touch responses.

There was a significant positive correlation between Baseline urine Uranium & taste, smell & touch responses. This means that uranium exposure is associated with taste, smell, and touch response impairment.

There was a significant positive correlation between Baseline urine Vanadium & body use, auditory response, taste, smell, touch responses, and Total CARS. This could indicate that vanadium exposure is associated with more impairment in body use, auditory response, taste, smell, touch responses and higher Total CARS.

There were statistical significant difference (Table 4), indicating that DMSA chelation treatment is beneficial in the reduction of different symptoms of autism such as:

- Relating to people
- Imitation
- Adaptation to change
- Taste, smell, touch, verbal
- Non-verbal communication
- Total score of CARS. ❑

DISCUSSION

The majority of patients in this study were boys (84%) as outlined in Table 1. This was in line with Whiteley et al (2010) (16) who noticed a greater preponderance of males over females (approximating 4:1) among autistic children.

The mean age of the whole sample was 5.11±1.57 (Table 1). This was consistent with Pervasive Developmental Disorder, which appears to affect children ages 3-10 years of age. (17)

Thirty-nine children were diagnosed as autistic, 2 (4.5%) as Asperger Syndrome, and 3 (6.9%) were diagnosed as PDD (NOS) (Table 1). This was consistent with Fombonne who claimed that autism is the most common of the Pervasive Developmental Disorders and is increasingly referred to as one of the Autism Spectrum Disorders (18).

In our group, the mean age of sitting was (6.77±0.96), crawling (10.41±1.65), walking (13.70±1.49), and talking (12.56±4.03) (Table 1). Filipek et al stated that in some cases autistic infants appear to develop normally until age 1 to 3 years. Then, sudden changes may occur that indicate the presence of ASD (19).

There were statistically significant difference between the baseline urine and DMSA challenge test regarding the level of cadmium, mercury, and lead (p=0.006, p=0.049, and p=0.008 respectively). Levels of cadmium, mercury, and lead were higher during the DMSA challenge test (mean=0.97±0.01, 16.12±36.57, 41.48±12.43 respectively) than the baseline urine level (mean=0.86±0.04, 3.35±3.81, 31.48±11.52 respectively) (Table 2). This was in line with Adams et al who stated that the severity of autism significantly correlated with the body burden of toxic metals as assessed through pre challenge tests (20).

	Reference range	Baseline urine		DMSA challenge test		p
		No.	Mean±SD	No.	Mean±SD	
Al	**>125**	5	322.76±216.19	6	331.65±213.76	0.947
As	**>50**	12	108.65±83.54	17	93.06±86.41	0.632
Cd	**>0.8**	4	0.86±0.04	5	0.97±0.01	**0.006**
Cr	**>3.5**	4	6.31±1.77	2	5.99±1.98	0.849
Hg	**>1.0**	31	3.35±3.81	43	16.12±36.57	**0.049**
Sb	**>1.0**	3	1.97±0.78	4	1.76±0.76	0.733
Ni	**>3.0**	43	12.17±9.91	43	11.97±8.89	0.922
Pb	**>5.0**	17	31.48±11.52	34	41.48±12.43	**0.008**
U	**>0.06**	7	0.169±0.103	5	0.134 ±0.098	0.567
V	**>1.4**	8	5.17±3.80	6	4.99±3.24	0.927

TABLE 2. Number of autistic children with high metals and metals level of baseline urine and DMSA challenge test urine.

		Al	As	Cd	Cr	Hg	Sb	Ni	Pb	U	V
Relating to people	R	-.222	.151	.182	-.205	.112	-.047	.066	.090	.190	-.092
	P	.147	.328	.236	.181	.468	.762	.670	.561	.254	.557
Imitation1	R	.029	-.114	.069	.124	-.049	.042	.019	.023	.027	-.102
	P	.854	.462	.657	.421	.751	.785	.903	.880	.870	.513
Emotional response	R	.068	.093	.059	.210	-.124	.081	.059	.051	.141	-.063
	P	.659	.550	.702	.171	.423	.603	.703	.742	.400	.687
Body use	R	.314	-.175	.107	.069	.114	.100	.085	.051	.179	.349
	P	**.038**	.257	.488	.654	.463	.519	.584	.742	.283	**.022**
Object use	R	-.285	-.210	.081	.384	.096	.216	-.148	.218	-.017	-.134
	P	.060	.172	.600	**.010**	.536	.158	.338	.156	.919	.391
Adaptation to change	R	.186	.017	.004	.136	.179	.081	-.156	.233	-.063	-.066
	P	.226	.911	.978	.377	.246	.604	.311	.127	.708	.673
Visual response	R	-.176	.012	.076	-.127	-.103	.111	.090	.057	.042	-.157
	P	.254	.938	.625	.410	.504	.473	.563	.713	.804	.314
Auditory response	R	-.257	-.288	-.160	.374	-.216	.201	-.102	.035	-.252	.345
	P	.093	.058	.301	**.012**	.159	.190	.508	.820	.127	**.023**
Taste, smell, touch response	R	.352	-.077	.431	.311	.299	.133	-.162	.075	.367	.522
	P	**.019**	.620	**.003**	**.040**	**.049**	.390	.294	.631	.023	**<.001**
Fear	R	.355	.128	.270	-.151	-.005	.079	.010	-.097	.202	-.226
Nervousness	P	**.018**	.409	.077	.329	.973	.610	.948	.532	.224	.145
Verbal communication	R	-.257	.313	.048	-.235	.014	.197	-.065	-.184	-.097	-.199
	P	.092	**.039**	.755	.125	.929	.201	.675	.232	.561	.202
Non-verbal communication	R	-.214	.195	.183	-.229	-.250	.056	-.033	.142	-.076	-.170
	P	.164	.204	.235	.134	.102	.716	.833	.359	.652	.276
Activity level	R	-.047	.100	-.010	.014	.106	.072	.080	.188	-.160	.068
	P	.762	.516	.947	.930	.492	.644	.606	.222	.336	.664
General impression	R	-.012	-.162	-.270	-.032	.140	.264	.005	.023	-.144	-.056
	P	.937	.295	.076	.834	.366	.084	.973	.882	.389	.719
Total CARS	R	.349	-.001	.165	-.262	.055	.269	-.091	.074	.035	.317
	P	**.020**	.993	.283	.085	.724	.077	.558	.633	.833	**.038**

TABLE 3. Correlation between Baseline Urine Toxic Metal Levels with the Subscales and Total Score of CARS.

Urine measurements before taking DMSA provide an indication of an immediate environmental exposure. Urine tests performed after the DMSA challenge reflect the accumulated or relative body burden (14,21,22).

DMSA therapy appears to be generally safe and effective in reducing specific symptoms of autism in some children (7). Bradstreet et al. investigated the body burden of toxic metals by giving DMSA and found that the urinary mercury excretion of children with autism was 3.1 times higher after the DMSA challenge (21). Lonsdale's findings indicate that detoxification treatment may have beneficial effects on some autistic children (25). Our data supports this.

In 2010, Yorbik et al linked Chromium, Cadmium and Lead levels in urine of children with autism (26). Bernard et al reported about mercury intoxication and its relation to autism (28). From our data we observed that the metals Aluminum, Cadmium, Chromium, Mercury, Uranium and Vanadium caused the most noticeably impairement with Taste, Smell and Touch Response being affected the most. In summary:

- Aluminum exposure affected Body Use, Fear and Nervousness, Taste, Smell and Touch Response and resulted in higher Total CARS. Aluminum causes oxidative stress within brain tissue and can exacerbate the clinical presentation of autism by worsening exitotoxicity and microglial priming (23).
- Arsenic affected Verbal Communication only (p=0.039). In 2005, Al-Ayadhi found significantly higher levels of arsenic and other metals (antimony, cadmium, lead and mercury) in children with autism spectrum disorder as compared to normal children (24).
- Cadmium only affected Taste, Smell and Touch Response (P = 0.003) Lonsdale et

al observed increased urinary cadmium, nickel and lead among children with pervasive mental disorder (25).

- Chromium affected Taste, Smell and Touch Response, Object Use & Auditory Response. Yorbik et al noticed similar findings (26).
- Mercury and Uranium could be linked to impairment in Taste, Smell and Touch Response only.
- Vanadium affected Body Use, Auditory Response and Taste, Smell and Touch Response

The results of this study support previous research, suggesting that toxic metals contribute to the severity of autism. Geier et al speculated that Autism may be "a combination of genetic/biochemical susceptibilities in the form of a reduced ability to excrete mercury and/or increased environmental exposure at key developmental times" (27). Bernard et al. hypothesized that postnatally exposed children develop articulation problems and show an inability to generate meaningful speech (28).

Our evaluation confirmed specific metals as neuro-developmental toxins, and we observed that a reduction in toxic metals is helpful in reducing some symptoms typically associated with autism. Through detoxification methods such as DMSA chelation, we reduced the severity of symptoms among our autistic group. ❑

RECOMMENDATIONS

Specific toxic metals affect the severity of symptoms typically seen in autism spectrum disorder, and we recommend that a larger study assesses the severity of autism symptoms, both before and after DMSA treatment. Such a study should include genetic tests such as the Glutathion S-transferases, because missing or nonfunctioning enzyme systems affect the body's natural detoxification mechanism. Research into the genetic make-up of the autistic population would enhance present knowledge about the far-reaching influence of toxins. Such a comprehensive study would provide much needed information on why toxins affect populations differently. It would also lend credibility to the notion that toxic metals influence autism severity and that detoxification therapy along with nutritional therapy provide a novel form of treatment to alleviate toxicity and autistic symptoms (29-31).

Item	Score before DMSA (mean±SD)	Score after chelation	p
Relating to people	2.17±0.38	2.5±0.65	0.005
Imitation	2.17 0.38	2.5±0.65	0.020
Emotional response	2.35±0.69	2.28±0.75	0.650
Body use	2.50±0.71	2.33±0.84	0.368
Object use	2.54±0.71	2.44±0.71	0.511
Adaptation to change	2.39± 0.5	2.42±0.76	0.048
Visual response	2.58±0.81	2.33±0.69	0.123
Auditory response	2.38±0.7	2.39±0.5	0.939
Taste, smell, touch	2.8±0.8	2.9±0.7	<0.001
Fear	2.23±0.71	2.22±0.73	0.948
Verbal communication	2.9±0.8	2.5±0.7	<0.001
Non verbal communication	2.6±0.7	2.4±0.7	<0.001
Activity level	2.65±0.56	2.39±0.7	0.17
Intellectual response	2.08±0.69	2.11±0.68	0.87
General impression	2.58±0.5	2.61±0.61	0.84
Total CARS	37.95±5.1	32.82±3.7	<0.001

TABLE 4. Comparison between CARS Subscales and Total Score before and after Chelation of 6 Months in the Whole Sample.

References

1. **Adams JB, Baral M, Geis E, et al. –** Safety and Efficacy of Oral DMSA Therapy for Children with Autism Spectrum Disorders: Part A - Medical results. *BMC Clinical Pharmacology* 2009; 9:1186-1472
2. **DeSoto MC, Hitlan RT –** Blood levels of Mercury are Related to Diagnosis of Autism: A Reanalysis of An important Data Set. *Journal of Child Neurology* 2007; 22:1308-1311
3. **Yorbik O, Kurt I, Hasimi A, et al. –** Chromium, Cadmium, and Lead Levels in Urine of Children with Autism and Typically Developing Controls. *Biol Trace Elem Res* 2010; 135:10-15
4. **Ballatori N, Clarkson TW –** Biliary Secretion of Glutathione and of Glutathione-Metal Complexes. Fundam. *Appl Toxicol* 1985; 5:816-31
5. **Ballatori N, Clarkson TW –** Dependence of Biliary Secretion of Inorganic Mercury on the biliary Transport of Glutathione. *Biochem Pharmacol* 1984; 33:1093-8
6. **Zalups RK –** Influence of 2,3-dimercaptopropane-1-sulfonate (DMPS) and meso-2,3- dimercaptosuccinic acid (DMSA) on the Renal Disposition of Mercury in Normal and Uninephrectomized Rats Exposed to Inorganic Mercury. *J Pharmacol Experim Therap* 1993; 267:791-800
7. **Adams JB, Baral M, Geis E, et al. –** Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: Part B -Behavioral results. *BMC Clinical Pharmacol* 2009; 9:1472-6904
8. **Soden SE, Lowry JA, Garrison CB, et al. –** 24-hour provoked urine excretion test for heavy metals in children with autism and typically developing controls, a pilot study. *Clin Toxicol* 2008; 45:476-481
9. **Kern JK, Geier DA, Adams JB, et al. –** Toxicity biomarkers in autism spectrum disorder: A blinded study of urinary porphyrins. *Pediatrics Intern* 2011; 53:147-153
10. **Blaurock-Busch E, Omnia R. Amin, et al. –** Toxic Metals and Essential Elements in Hair and Severity of Symptoms among Children with Autism. *Maedica* 2012; 7:38-48
11. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, Wash 1994
12. **Schopler E, Reichler RJ, Renner BR –** The Childhood Autism Rating Scale.: Western Psychological Services. Los Angeles, CA 1994
13. **Matson JL, Smiroldo BB, Hastings TL –** Validity of the Autism/Pervasive Developmental Disorder subscale of the Diagnostic Assessment for the Severely Handicapped-II. *J Autism Dev. Disord* 1998; 28:77-81
14. **Blaurock-Busch E –** Toxic Metals and Antidotes. Chelation Therapy Handbook. *MTM Publ* 2012; 55-56
15. **Knapp RG, Miller MC –** *Clinical Epidemiology and Biostatistics* 1992; 13:187-195
16. **Whiteley P, Todd L, Carr K, et al. –** Gender Ratios in Autism, Asperger Syndrome and Autism Spectrum Disorder. *Autism Insights* 2010; 2:17-24
17. Diagnostic and Statistical Manual of Mental Disorders. DSM-IV-TR American Psychiatric Association Washington, DC 2010
18. **Fombonne E –** Epidemiology of autistic disorder and other pervasive developmental disorder. *J Clin Psych* 2005; 66:3-8
19. **Filipek PA, Accardo PJ, Baranek GT, et al. –** The Screening and Diagnosis of Autism Spectrum Disorders. *J Autism Developm Disorders* 1999; 29:439-484
20. **Adams JB, Baral M, Geis E, et al. –** The Severity of Autism Is Partially Explained by Toxic Metal Body Burden and Red Blood Cell Glutathione Levels. *J Toxicol* 2009; 10:640-647
21. **Bradstreet J, Geier DA, Kartzinel JJ, et al. –** A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders. *Journal of American Physicians and Surgeons* 2003; 8:76-79
22. **Zalups RK –** Influence of 2,3-dimercaptopropane-1-sulfonate (DMPS) and meso-2,3- dimercaptosuccinic acid (DMSA) on the Renal Disposition of Mercury in Normal and Uninephrectomized Rats Exposed to Inorganic Mercury. *J Pharmacol Experim Therap* 1993; 267:791-800
23. **Blaylock RL, Strunecka A –** Immune-glutametric Dysfunction as A central Mechanism of the Autism Spectrum Disorders. *Curr Med Chem.* 2009; 16:157-70
24. **AL-Ayadhi L –** Heavy Metals and Trace Elements in Hair Samples of Autistic and Normal Children in central Saudi Arabia. *Neurosciences* 2005; 10:213-218
25. **Lonsdale D, Shamberger RJ, Audhya T –** Treatment of Autism Spectrum Children with Thiamine Tetrahydrofurfuryl Disulfide: A pilot Study. *Neuroendocrinol* 2002; 23:303-8
26. **Yorbik O, Kurt I, Hasimi E, et al. –** Chromium, Cadmium, and Lead Levels in Urine of Children with Autism and Typically Developing Controls. *Biol Trace Ele Res* 2010; 135:10-15
27. **Geier DA, Kern JK, Garver CR, et al. –** Biomarkers of Environmental Toxicity and Susceptibility in Autism. *J Neurol Sci* 2009; 280:101-108
28. **Bernard S, Enayati A, Redwood L, et al. –** Autism: A novel form of Mercury Poisoning. *Binstock Med Hypotheses* 2001; 56:462-471
29. **Adams JB, Baral M, Geis E, et al. –** The Severity of Autism Is Associated with Toxic Metal Body Burden and Red Blood Cell Glutathione Levels. *J Toxicol* 2009; 26:532-640
30. **Adams JB, Holloway C –** Pilot Study of A moderate Dose Multivitamin/ Mineral Supplement for Children with Autistic Spectrum Disorder. *J Altern Complement Med* 2004; 10:1033-9
31. **Stein J, Schettler T, Wallinga D, et al. –** In: Harm's Way: Toxic Threats to Child Development. *J. Dev-Behav. Pediatr.* 2002; 23:13-22.